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Enantioselective synthesis of bicyclic compounds *via* catalytic 1,4-addition-ring closing metathesis†

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A novel three step asymmetric annulation procedure comprises a tandem catalytic enantioselective 1,4-addition-allylic substitution, Grignard addition and ring closing metathesis (RCM) sequence to provide [6,6], [7,6], [8,6] and [6,7] bicyclic products with ee's of 93–97% in which the size of both rings can easily be varied independent of each other.

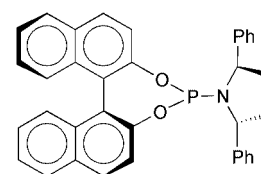
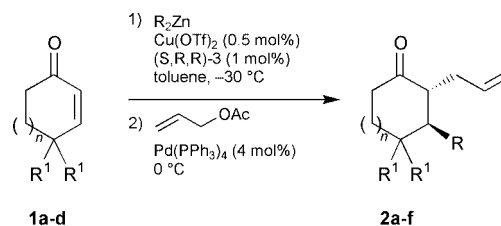
Novel routes to carbobicyclic compounds in enantiomerically pure form continue to offer a synthetic challenge since numerous products including terpenes and steroids show this structural feature. A classical example is found in the synthesis of (±)-D-homo-19-nortestosterone starting from the readily available Wieland–Miescher ketone for which an asymmetric synthesis proceeds *via* the Hajos–Parrish version of the Robinson annulation.^{1,2} In the pursuit of novel catalytic asymmetric annulation strategies we focus on the construction of enantiomerically pure carbobicyclic products with various ring sizes.³

Since the pioneering work by the groups of Grubbs and Schrock, ring closing metathesis (RCM) has become a powerful tool for the synthesis of a variety of cyclic structures.⁴ Especially for medium sized and macrocyclic ring systems, which are difficult or even impossible to make by other methods, RCM proved to be highly valuable.⁵ As a result of the remarkable tolerance of the Grubbs catalyst towards various functional groups, RCM is increasingly applied in natural product synthesis.⁶

We envisioned that by making use of a combination of RCM and the copper–phosphoramidite based catalytic enantioselective 1,4-addition developed in our laboratories, a variety of enantiomerically pure bicyclic products would become readily accessible. In these bicyclic products both ring sizes can easily be varied, independent of each other. The following considerations were made: (i) cyclic enones with different ring sizes and substituents can be employed in the catalytic 1,4-addition with enantioselectivities generally exceeding 96% in the products. These products can subsequently act as templates onto which a second ring can be annulated.⁷ (ii) The use of RCM for this annulation would make different ring sizes in the second ring possible.⁸

To examine the viability of this approach we synthesized 2-allyl-3-alkylcycloalkanones **2a–f** by a tandem 1,4-addition-allylic substitution reaction.^{3,9}

As is shown in Scheme 1 the zinc enolate resulting from the catalytic 1,4-addition of dialkylzinc reagent to cycloalkanones in the presence of phosphoramidite ligand (*S,R,R*)-**3** (1 mol%) and Cu(OTf)₂ (0.5 mol%) was trapped stereo- and regioselectively by the Pd–allyl complex *in situ* generated from allyl acetate and a catalytic amount of Pd(PPh₃)₄, giving disubstituted cycloalkanones **2a–f** in good yields and with ee's ranging from 93 to 97% (Table 1). Furthermore a *trans*–*cis* ratio of 9:1 or higher is observed in all cases except for **2e** (entry 5).¹⁰ In the case of **2b** and **2d** complete diastereoselectivity towards the *trans* isomer is found.



(*S,R,R*)-**3**

Scheme 1

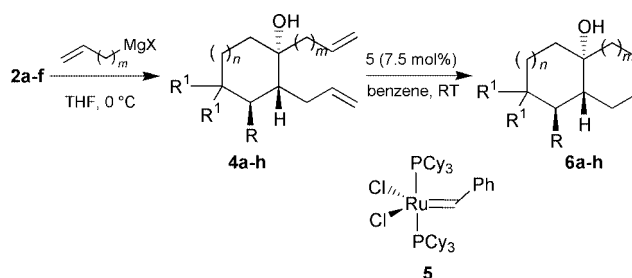
Table 1 Tandem-1,4-addition-allylic substitution to cyclic enones.

Entry	Enone	<i>n</i>	R ¹	R	C.y. 2 (%) ^a	ee 2 (%) ^b	<i>trans</i> – <i>cis</i> ^c
1	1a	1	H	Et	2a 88	96	9:1
2	1b	2	H	Et	2b 86	— ^d	— ^e
3	1c	3	H	Et	2c 79	97	196:1
4	1d	1	Me	Et	2d 82	— ^d	— ^e
5	1a	1	H	Me	2e 92	96	5.3:1
6	1a	1	H	Bu	2f 83	93	9:1

^a Isolated yield after column chromatography. ^b Determined by chiral GC (Chiraldex G-TA). ^c Determined by GC. ^d Not determined. ^e Only *trans* detected.

By introducing a second terminal alkene moiety *via* the 1,2-addition of suitable Grignard reagents such as vinyl-, allyl- and butenylmagnesium halides to **2a–f**, the corresponding dienes **4a–h** are formed which are next converted to carbobicyclic structures **6a–h** by RCM as is shown in Scheme 2.

Table 2 summarizes the results of this new enantioselective method for the preparation of carbobicyclic structures. As expected, a reasonable selectivity was observed for the addition



Scheme 2

† Electronic supplementary information (ESI) available: NMR spectra and detailed explanation. See <http://www.rsc.org/suppdata/cc/b1/b100283j/>

Table 2 Grignard addition and RCM

Entry	R	R ¹	<i>n</i>	<i>m</i>	C.y. 4^a (%)	ee 4^b (%)	Ring system	C.y. 6^d (%)	ee 6^b (%)			
1	2a	Et	H	1	1	4a	92	— ^c	6a	[6,6]	60	96
2	2b	Et	H	2	1	4b	68 ^d	96	6b	[7,6]	100	96
3	2c	Et	H	3	1	4c	95	97	6c	[8,6]	43	97
4	2d	Et	Me	1	1	4d	70	— ^c	6d	[6,6]	79	97
5	2e	Me	H	1	1	4e	82	— ^c	6e	[6,6]	46	96 ^e
6	2f	Bu	H	1	1	4f	92	— ^c	6f	[6,6]	68	93
7	2a	Et	H	1	0	4g	64	— ^c	6g	[6,5]	— ^f	—
8	2a	Et	H	1	2	4h	98	— ^c	6h	[6,7]	65	96

^a Isolated yield as a mixture of diastereomers. ^b Determined by chiral GC (Chiraldex G-TA). ^c Not determined. ^d Isolated yield of all-*trans* isomer after column chromatography. ^e Determined by chiral HPLC after conversion into the *p*-nitrobenzoate ester. ^f Only a small amount (<10%) of *cis*-fused **6g** was detected by GC.

of the Grignard reagents to **2a–f** in all cases and the major isomer results from the attack of the Grignard reagent *trans* to the allyl group leading to the all-*trans* isomer as the major product (Scheme 2). Addition of allylmagnesium chloride (*m* = 1, entry 1) to a 90:10 *trans*–*cis* mixture of **2a** yields three out of four possible diastereomers of **4a** in a ratio of 74:16:10 as judged by GC. This result is explained as follows: addition of the Grignard reagent to the *trans* compound (2*R*,3*S*)-**2a** proceeds preferably *trans* to the allyl group but not with complete selectivity accounting for 74% (1*R*,2*R*,3*S*)-1,2-diallyl-3-ethylcyclohexanol (**4a**) and 16% (1*S*,2*R*,3*S*)-**4a**. The relative configuration of the major isomer was determined by COSY, HSQC and NOESY NMR experiments on the *p*-nitrobenzoate ester of **6a**.[†] Addition to the minor *cis* compound (2*S*,3*S*)-**2a** accounts for the 10% of another isomer of **4a**, most probably (1*S*,2*S*,3*S*)-**4a**.

In the case of *trans*-**2b** the ratio of *trans* and *cis* addition is 80:20 and pure *trans*-**4b** (68%) could be isolated by column chromatography. The addition to *trans*-**2c** proceeds with a moderate selectivity giving a *trans*:*cis* ratio of 63:37. Addition of butenylmagnesium bromide (*m* = 2) to a 9:1 *trans*–*cis* mixture of **2a** in THF at 0 °C required transmetalation to the organocerium reagent to prevent enolization and to give complete conversion to **4h** as a mixture of 3 isomers (87:12:1) with (1*R*,2*R*,3*S*)-**4h** as the major product (entry 8).¹¹

All dienes **4a–h** readily undergo ring closure in benzene in the presence of 7.5 mol% of Grubbs catalyst **5**, except for **4g**. In the latter case formation of only a small amount of **6g** was observed (entry 7). GC analysis revealed that only the *cis* isomer of **4g** had been converted. The *trans*-fused 5,6-ring system is not formed, most probably due to the strain in such a system.¹² Formation of a six membered ring (entries 1–6) proceeded well in all cases as 100% conversion was observed, indicating that both *cis*- and *trans*-fused ring systems are readily formed. Isomerically pure *trans*-diene **4b** provided the 7,6-bicyclic product in 100% isolated yield. In all other cases the major isomer of the resulting carbobicyclic products from this annulation protocol was isolated in moderate to good yield by simple chromatographic procedures with ee's ranging from 93 to 97%. For example, (1*S*,9*R*,9*aR*)-**6a** could be isolated in 60% yield. Annulation of a seven membered ring by RCM was also successful as (1*S*,4*aR*,9*aR*)-**6h** with an ee of 96% was isolated in 65% yield (entry 8).

In conclusion, new methodology for the synthesis of enantiomerically pure carbobicyclic compounds has been developed, based on an enantioselective tandem 1,4-addition–allylic substitution, Grignard addition and RCM three step sequence. In contrast to most methodologies for asymmetric annulations, which are restricted to specific ring sizes, the method presented here gives high enantioselectivities for the construction of a variety of bicyclic structures. Products with

[6,6], [7,6], [8,6] and [6,7] carbobicyclic skeletons and different alkyl substituents have been prepared with ee's ranging from 93–97%.

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